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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,333	BERLIN, KATHRIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 4/8/04. Claims 1, 6, 7, 8, 9, 10, 11, 13, 15, 16, 17, 18, 19, 20, 25, 26, and 27 have been amended. Claims 1-29 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is non-final.**

2. The examiner prosecuting the application has changed. Please address future correspondence to Juliet Switzer, Art Unit 1634.

Claim Objections

3. Applicant is advised that should claim 9 be found allowable, claim 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. Claims 2, 4, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 25, are 28 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite over the recitation "used and indicted" because it is not clear what the positions are being "used" for as claim 1 does not recite the "use" or "indication" of particular positions. Applicant is advised to use claim language that is consistent with that of claim 1.

In claim 4, the recitation "the reagent for selective conversion of cytosine to uracil" lacks proper antecedent basis because claim1, while reciting a reagent, does not recite a reagent "for selective conversion of cytosine to uracil.

Claims 6 and 7 are indefinite because they refer to "the genomic DNA," but it is not clear to which genomic DNA they are intended to refer because claim 1 recites a sample genomic DNA and a reference genomic DNA so it is not clear which is "the" genomic DNA. Claims 9 and 10 are also indefinite over this recitation as they depend from claim 6.

Claim 7 is indefinite over the recitation "in step d) by formation of heteroduplexes with a completely methylated reference DNA," because step (d) does not require a completely unmethylated reference DNA, only a reference genomic DNA, and so if applicant is intending to require here that step (c) of claim 1 must use a unmethylated DNA or if somehow between step (c) and (d) the DNA is unmethylated, etc.

In claim 11, the phrase "the location and/or presence of cleaved...positions" lacks proper antecedent basis in the claim because the claims do not previously recite a cleaved position, therefore it is confusing which cleaved position applicant is referencing. Claims 12-17 are also indefinite over this recitation because they depend from claim 11.

Claim 17 is indefinite because it is not clear what it means to position PCR primers "newly stepwise by the maximally detectable range." It is not clear how primers are positioned by a range of a mass spec, etc. Clarification is required.

Claim 25 is confusing. It is not clear how this claim is meant to further limit claim 1. It is not clear if the claim intends for each of steps (a) to (f) to be repeated in view of the "such that" clause that only recites the repetition of steps (a)-(c). Further the claim requires that a genomic DNA of step (c) is treated according to steps (a) and (b), but claim 1 already appears to require such a step, as step (c) of claim 1 requires that steps (a) and (b) are preformed on a reference genomic DNA. Finally, it is not clear what is meant by "the genomic DNA of (a) is treated according to step (c)." It is not clear if applicant is intending to set forth that the "sample" genomic DNA of step (a) is the same as the "reference" genomic DNA of step (c) or some other limitation. The recitations of claim 25 appear to merely restate steps that are already present in claim 1.

Claim 28 is indefinite over the recitation "as different as possible" because it is not clear what this modifies, for example, the DNA, the individuals, the cells, the cell lines, etc. Furthermore, it is not clear what "as different as possible" means in this claim, as different as possible with regard to what feature/features?

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 18, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claim 16, the new limitation that primers are "sequential, staggered, consecutive, or overlapping to other PCR primers" appears to be new matter. The specification discusses a series of PCR reactions using primers "set stepwise" (third paragraph page 9) but does not appear to provide basis for sequential, staggered, consecutive, or overlapping PCR primers. The specification does not clearly define what is meant by "set stepwise" and thus this phrase does not appear to provide basis for the newly added limitation.

In claim 18, the new limitation of "that enables the polymerase reaction to be immobilized" in claim18 appears to represent new matter. While claim 18 provides basis for a primer that would enable a PCR product to be immobilized on a surface, there does not appear to be any support for a method that enables the polymerase reaction itself to be immobilized on a solid support.

In claims 26 and 27 the requirement in part (b) of both claims that "one primer of the polymerase reaction is fluorescently labeled and provided with a chemical function thereby enabling the immobilization of the amplificate on a surface" appears to be new matter. The specification does not appear to provide for such primers. The specification discusses labeled

products and products that can be immobilized, but does not discuss primers modified as required by claims 26 and 27 herein.

No specific basis for these limitations was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112

6. Claims 6, 9, and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 6 is drawn to a method for detecting the presence of 5-methylcytosine positions in a sample genomic DNA, and requires a step of chemical modification of the genomic DNA and formation of heteroduplexes with a reference such that "erroneous base pairs are produced in the positions at which a 5-methylcytosine was located in the genomic DNA."

The specification teaches methods in which bisulfite treatment is used to convert all unmethylated cytosines to uracil, and thus a resulting erroneous base pair would be produced in the positions at which thee were unmethylated cytosines (p. 7, second paragraph). The specification teaches that additional possible reagents for use in the claimed methods are hydrazine and permanganate, but neither of these would result in an erroneous base pair at a position at which a 5-methylcytosine was located in the genomic DNA. There are no working examples that provide a method in which erroneous base pairs are produced in the positions at which a 5-methylcytosine was located in the genomic DNA.

The prior art at the time of the invention does not provide a chemical treatment as required by step (a) of the claim that would result in an erroneous base pairs are produced in the positions at which a 5-methylcytosine was located in the genomic DNA. Permanganate treatment is a treatment which selectively modifies methylated cytosines, but it does not result in a base change that would cause an erroneous base pairing. Rein *et al.* (as cited in IDS) provide a review of methods for detecting methylated cytosines and teach that permaganate is a routine method for selectively modifying methycytosine, but resultant primer extension following the modification would not result in a mismatch but instead in a non-extended sequence (see Table 1; also p. 2261 and Figure 3).

It is highly unpredictable what chemical modification could result in the chemistry required by claim 6, and claims 9 and 10 which depend from claim 6, as no such chemistries are known. The discovery of such a method would require extensive experimentation and screening to discover such a method.

Thus, in view of these factors, it is concluded that it would require undue experimentation to practice the claimed invention which requires that erroneous base pairs are produced in the positions at which a 5-methylcytosine was located in the genomic DNA.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 28 and 29 rejected under 35 U.S.C. 102(e) as being anticipated by Nazarenko *et al.* (US 6090552).

The rejected claims are drawn to kits.

Claim 28 requires that the kit comprise DNA of at least two individuals, tissues, cell lines, or cells that are "as different as possible," along with reagents to indicate the variable methylation positions. Nazarenko *et al.* teach a kit comprising methylated control DNA and unmethylated control DNA. These two DNA molecules are "as different as possible" with regard to methylation status. The kit taught by Nazarenko *et al.* also includes reagents for amplification and sodium bisulfite for indicating variable methylation positions.

Claim 29 requires that the kit contains completely methylated and/or demethylated DNA and reagents. Herman *et al.* Nazarenko *et al.* teach a kit comprising methylated control DNA and unmethylated control DNA. The kit taught by Nazarenko *et al.* also includes reagents for amplification and sodium bisulfite for indicating variable methylation positions.

Thus, the kits taught by Nazarenko *et al.* anticipate the instant claims.

Claim Rejections - 35 USC § 103

9. Claims 1-5, 7-8, 11, 18-25, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rice *et al.* (Oncogene (1998) 17, 1807-1812) in view of Gifford (US 5750335).

Rice *et al.* teach a method for identifying 5-methylcytosine positions in a sample genomic DNA, said method comprising the steps of:

(a) chemically treating a sample genomic DNA obtained from at least one cell in such a way that cytosine and 5-methylcytosine react differently and from products with different base pairing behavior (p. 1811, treatment with sodium bisulfite);

(b) amplifying by means of a polymerase reaction a segment of the genomic DNA obtained in step (a) (p. 1811, second column);

(c) performing steps (a) and (b) on a reference genomic DNA (Figure 3, methylation was determined for eight different cell types);

Rice *et al.* utilize chemical treatment with sodium bisulfite in a method to identify the location of methylated cytosines in genomic DNA. Treatment with bisulfite results in the conversion of unmethylated cytosine residues to uracil, while methylated cytosine residues remain unchanged. Thus, in a sample with unmethylated sequence (for example the HMEC) there would be no change in sequence, but in a sample with high levels of methylation, after PCR there would be thymines where the methylated cytosines previously were located. Rice *et al.* effectively introduce mutations nucleic acid sequences via the treatment with sodium bisulfite. Rice *et al.* utilize a sequencing method to determine the methylation positions after amplification of the sequences.

With regard to claim 2, in the method taught by Rice *et al.* positions which are variable between different cell lines are identified (see figure 3).

With regard to claim 3, Rice *et al.* utilize a bisulfite to treat the genomic DNA.

With regard to claim 4, Rice *et al.* jointly amplify genomic DNA from several cells, as they necessarily isolated DNA from more than one cell for each cell line.

With regard to claim 5, Rice *et al.* separately amplified the DNA from several cell lines, and then treated them all by amplification.

With regard to claim 7, the introduction of erroneous base pairs occurs at positions at which cytosine was located in the genomic DNA.

With regard to claim 8, Rice *et al.* test unmethylated cell lines (p. 1807, second column; Figure 3).

With regard to claim 18, a nucleotide sequence is considered a "chemical function" that enables a PCR reaction or product to be immobilized on a surface. Therefore, the PCR carried out by Rice *et al.* necessarily uses a primer that enables the polymerase reaction to be immobilized on a surface. The claim does not actually require an immobilization step.

With regard to claim 25, Rice *et al.* teach treating and amplifying a reference genomic DNA as in steps (a) and (b) for a number of "reference" sequences.

Rice *et al.* do not form heteroduplexes from the amplified products for the comparison of a test and reference sample. With regard to claims 28 and 29, Rice *et al.* teach DNA samples from different cells, some that are methylated and some that are not (as different as possible from one another) and reagents for detecting methylation status in samples. Rice *et al.* do not teach kits.

Gifford teaches a method for identifying sequence differences between two nucleic acids that comprises the steps of:

(d) forming heteroduplexes from two different nucleic acid samples (Col. 3, lines 40-50);

(e) introducing a detectable label into the heteroduplexes of step (d) by means of a reaction which is specific for non-complementary base pairs (Col. 4, lines 15-20), and

(f) determining the position of 5-methylcytosine in the sample genomic DNA based on the presence and position of the detectable label (Col. 4, lines 5-10, 20-25).

Gifford specifically teaches comparing a sample (patient) nucleic acid fragment with a control (normal) nucleic acid fragment (Figure 2).

With regard to claims 4 and 5, Gifford teaches that a test or reference nucleic acid may include monoclonal or polyclonal cell lines (Col. 9, 22-25).

With regard to claim 11, Gifford teach detecting the presence of bound DNA via agarose gel electrophoresis, thus determining the presence of the labeled positions (Col. 13, lines 33-45).

With regard to claims 19, Gifford teaches that the reference or test nucleic acids may be immobilized to a solid surface (Col. 5, lines 1-5; col. 13, lines 1-5). With regard to claim 20, Gifford teaches that "different" reference nucleic acids may be immobilized on a solid surface at different spots, which are considered different reaction vessels (Col. 5, lines 1-5). Further, Gifford teaches the transfer of the amplified products to different vessels (affinity columns or affinity matrix) for purification of the heteroduplexes wherein the products are coupled to a solid support (column 5, lines 47-56).

With regard to claim 21 and 22, Gifford teaches an using an enzyme that forms a complex with a non-complementary base pair (Col. 4, lines 10-20), specifically teaching MutS (Col. 7, line 22).

With regard to claim 23, Gifford teaches a method wherein the enzyme bears a label by which a complex can be displayed (Col. 15, lines 65-67).

With regard to claim 24, Gifford teaches that the label is a fluorescence label (Col. 15, lines 65-66).

With regard to claims 28 and 29, Gifford teaches kits comprising reagents for comparison of a test and reference nucleic acid, which include reagents to detect mismatches, reference nucleic acids, etc.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methylation detection method taught by Rice *et al.* so as to have utilized the mutation detection methods taught by Gifford. One would have been motivated to utilize the methods taught by Gifford in order to achieve the express benefits of the methods taught by Gifford which include achieving "rapid and accurate genetic screening and diagnosis by comparing two nucleic acids for differences in their sequences...to locate previously unknown mutations of a nucleotide sequence, and to identify the sequence itself, where the nature and position of the mutation within a region of the genome is unknown, and where the location of the region itself is unknown (Col. 3, lines 25-40)." Furthermore, it would have been prima facie obvious to one of ordinary skill in the art to have included reagents taught by Rice *et al.* in a kit as taught by Gifford in order to have provided one with a set of reagents for the practice of the method.

10. Claims 12, 13, 14, 15, 16, 17, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rice *et al.* in view of Gifford as applied to claims 1-5, 7-8, 11, 18-25, 28, and 29 above, and further in view of Koster *et al.* (US 6428955).

The teachings of Rice *et al.* in view of Gifford are applied herein as applied in the previous rejection. In the method taught by Rice *et al.* in view of Gifford, sodium bisulfite is used which results in the modification of unmethylated cytosines, and therefore mismatches would occur at positions where cytosine was located in the genomic DNA. Rice *et al.* in view of

Gifford do not teach a method in which the heteroduplex is detected by cleavage of the heteroduplex molecule or in which mass spectrometry is used to analyze the size of the DNA fragments.

With regard to claims 12-14, Koster *et al.* teach methods for analyzing the size of nucleic acid fragments using mass spectrometry, specifically teaching the use of MALDI-TOF and ESI, (Col. 18, line 66-Col. 19, line 11).

With regard to claim 15, which requires that the nucleic acids in step (e) are "adapted" to the performance capacity of the mass spectrometer, Koster *et al.* teach utilizing a variety of PCR amplification methods to obtain PCR products that they analyze using the mass spec (See examples 14-15, for example). With regard to claim 16, Koster *et al.* teach utilizing nested PCR to amplify products for detection (Examples 5 and 14, for example), a method which uses primers that are staggered along the DNA with respect to the inner and outer pairs of primers and produce a series of amplification products, at least one which is within the mass range detectable by means of mass spectrometry. With regard to claim 17, the outer primers of a nested PCR make a larger product with is stepwise larger than the inner PCR product and the outer PCR product is closer to the maximally detectable range of the mass spectrometer.

Claim 26 differs from claim 1 in that in step (b) a primer used in the PCR is fluorescently labeled and provided with a chemical function thereby enabling the immobilization of the amplificate on the surface, step (e) utilizes a chemical mismatch cleavage methodology, and step (f) utilizes mass spectrometry, whereby in step (g) the presence or presence and position of the 5-methycytosine within the genomic DNA is deduced from the length of the cleaved nucleic acids. Claim 27 is similar to claim 26 but requires that a detectable label is introduced into the

heteroduplex by an enzymatic reaction which is specific for non-complementary base pairs. This limitation is provided in the methods taught by Rice *et al.* in view of Gifford.

Koster *et al.* teaches a method in which a heteroduplex is cleaved by an agent that cleaves the unhybridized portion so that a mismatch results in two products and then detecting these by mass spectrometry to detect the presence of the mismatch (Col. 5, lines 30-40; Col. 23, lines 25-40). Koster *et al.* further teach primers that are labeled with biotin (a means for immobilizing an amplificate on a surface; col. 35, for example) and primers that are labeled with a radioactive label and oligonucleotides that are fluorescently labeled (Col. 49, for example). In addition, as noted previously in this office action, any nucleic acid sequence itself is considered a "chemical function" that would enable the immobilization of the amplificate on a surface. Claims 26 and 27 never actually require the immobilization of the amplificate on a surface, only that such immobilization is "enabled." Nonetheless, Koster further teach methods in which the sequence to be detected is immobilized to a solid support by means of hybridization (Col. 3, lines 60-67).

It would have been prima facie obvious to one of ordinary skill in the art to have modified the method taught by Rice *et al.* in view of Gifford *et al.* so as to have used the amplification and detection methods taught by Koster *et al.* One would have been motivated to use mass spectrometry as a means for detection of nucleic acid fragments in order to take advantage of the express benefits of such a method as taught by Koster *et al.*, who state "the processes of the invention provide for increased accuracy and reliability of nucleic acid detection by mass spectrometry (Col. 5, lines 62-65). Furthermore, it would have been prima facie obvious to have utilized fluorescently labeled primers in place of the radioactively labeled

primers taught by Koster *et al.* in order to have provided an alternative labeling method that is safer to use as opposed to using radioactivity in the laboratory.

Response to Remarks

The prior art rejections from the previous office action have been withdrawn. While the examiner feels the previous prior art rejections would have been maintainable, the rejections are withdrawn in view of what the examiner feels are clearer rejections. Thus, in light of the new grounds of rejection this office action is non-final. Nonetheless, the remarks set forth by applicant in the response are addressed insofar as they might apply to the instantly set forth rejections.

The 112 2nd paragraph rejections set forth in the previous office action are overcome by applicant's extensive amendments to the claims. New 112 2nd rejections are set forth to address the amended claims

The 103 rejection over Gifford in view of Herman is withdrawn. Applicant traverses the rejection stating that there exists a long-felt need for novel methods for the simple, cost-effective, and time-effective detection and analysis of cytosine methylation (remarks, p. 19). This is not persuasive to overcome the newly set forth rejection. In order to establish long-felt need in the art, applicant must demonstrate evidence of the following: First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. Second, the long-felt need must not have been satisfied by another before the invention by applicant. Third, the invention must in fact satisfy the long-felt need (see MPEP 716.04). Applicant has not met this burden. As a preliminary point, there is no evidence provided on the record of a long felt need,

only an attorney argument. Arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Further, turning to the three points regarding long-felt need set forth in MPEP 716.04, even if applicant were to establish that there was a persistent need recognized by one of skill in the art for methylation detection methods, the prior art of record in this application demonstrates that there were alternative methods known for satisfying the long felt need. Therefore, this argument is not persuasive to overcome the prima facie case of obviousness set forth herein.

Applicant's arguments against Gifford alone are piecemeal in nature and do not consider the totality of the rejection (first ¶, p. 20). In the combination presented herein, Rice *et al.* provide for methods of detection of methylation. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

On page 20 of the response applicant discusses the nature of the claimed invention in general but does not address any further arguments with regard to the previous obviousness type rejection.

On p. 21 applicant points out that the instant invention is a basic research tool that enables the identification of differentially methylated positions between groups of tissues and the discovery of methylation markers. The methods taught by Rice *et al.* in view of Gifford also meet this goal.

With respect to claims 28 and 29 it is first noted that new 102 rejections are set forth herein to address these claims. They are also rejected as being obvious. Applicant does not present any arguments with regard to these claims in particular to support their non-obviousness. Thus, the 103 rejection is set forth against these as well, for the reasons given in the rejection.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Juliet C Switzer
Examiner
Art Unit 1634

June 11, 2004